EXHIBIT 21

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GENERAL ADULT PSYCHIATRY

DIPLOMATE AND EXAMINER AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

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Re: Case No.: 3:17-CV-00783-MJR-SCW, *D. B., a Minor* by *Irina Liona Burnett, Individually as Parent and Next friend of D.B. vs. Abbott Laboratories, Inc., et al.,* In the United States District Court for the Southern District of Illinois

Dear Mr. Ball and Mr. Mallen,

Thank you for asking me to review medical records, depositions, and other materials regarding Ms. Irina Burnett, a 49-year-old woman, in the above-referenced matter. By way of background, qualifications, and experience, I am a physician licensed to practice medicine in Texas. As a psychiatrist, I specialize in areas of mental health and mental illnesses, including an emphasis on the study and treatment of schizoaffective disorder and mood disorders such as bipolar disorder. I am board-certified in psychiatry by the American Board of Psychiatry and in past years, have served as a Part II Oral Examiner for the American Board of Psychiatry and Neurology. I currently hold an appointment as an Adjunct Professor of Psychiatry at the University of Texas Health Science Center in San Antonio, where I completed my residency training in 1986 and served one year as Chief Resident in the department. I have remained on the clinical faculty of the University of Texas Medical School for the past thirty years and continue to teach residents and medical students on a regular basis.

After graduating from Southern Methodist University in Dallas, Texas in 1977 with a major in biology and a minor in biomedical engineering, I conducted graduate studies as a research student at Southwestern Medical School in Dallas, where I specialized in the neurology and physiology of the central regulation of human body temperature and fever. I received my Doctor of Medicine degree from the University of Texas Health Science Center in San Antonio in 1982.

I have treated hundreds of patients in my career with a diagnosis of schizoaffective disorder and/or bipolar disorder, such as with patients like Irina Burnett, who was diagnosed and treated for a severe form of schizoaffective disorder, depressive type (295.70). I have treated many women with schizoaffective disorder and bipolar disorder during their childbearing years. I have also treated many patients who not only have a mental health disorder such as schizoaffective disorder or bipolar disorder, but also have a seizure disorder or a potential seizure disorder, like Irina Burnett.

I am familiar with the standard of care in providing medical treatment in such cases. I also have substantial experience and qualifications in evaluating the warnings of medicines for use by psychiatrists, including myself, to counsel patients and make informed prescribing decisions. I have taught medical students and residents about warnings, including regarding Depakote and other medicines. I also have given presentations to the medical community about package inserts, including Depakote, and issues related to informed consent.

In addition to providing psychiatric treatment, medication management, and counseling therapy for thousands of patients, I have given numerous presentations regarding the evaluation, treatment, and long-term outcomes of patients with schizoaffective disorder, bipolar disorder, and depression. I have published a number of articles regarding the subject of depression. I have written or renewed thousands of prescriptions each year for medicines used to treat patients with schizoaffective disorder, bipolar disorders, and depression. The opinions I express in this report are based on my background, education, training, and professional experience and are based on a reasonable degree of medical certainty.

It is not uncommon (and especially so in 1999) in the field of psychiatry to treat patients with both mental illnesses and particular seizure disorders. It is not uncommon in the field of psychiatry (including in my practice) to change a patient's medications for mental illness because the patient has a seizure disorder (or potential seizure disorder) including having an abnormal EEG. As further discussed below, that is this case. Ms. Burnett's treating psychiatrist, Dr. Al C. Edwards, prescribed Depakote to Ms. Burnett as a dual purpose treatment for a possible seizure disorder and a bipolar-type component of schizoaffective disorder.

Seizures are a serious epileptic condition. As with schizoaffective disorder or bipolar disorder, seizures involve serious risks to the patient and others and can interfere with employment, schooling, and relationships. Seizures during pregnancy are never safe and can lead to injury or death in the patient and fetus.

While schizoaffective disorder and bipolar disorder are different conditions, they can have similar and overlapping symptoms. Schizoaffective disorder is a severe mental illness that often includes patients who have profoundly disturbing hallucinations, delusions, and paranoia. Patients with schizoaffective disorder often have erratic and sometimes dangerous mood swings that interfere with cognitive and emotional functioning. Schizoaffective disorder patients rarely remit, meaning they typically do not have breaks in their illness or times when they do not have psychotic thinking.

Patients with schizoaffective disorder can have mood swings that resemble the severe manic and depressive episodes of bipolar disorder that can lead to profound suicidal obsessions and psychotic, out-of-touch with reality delusions, such as with Ms. Burnett. Such symptoms can and often do lead to life-threatening behaviors to the patient and to others. Patients with schizoaffective disorder

like Irina Burnett can have psychotic and paranoid delusions leading to her wanting to stab herself and/or her child. Regardless of intensive treatment, patients with schizoaffective disorder progressively and tragically usually worsen over time. It is often a disabling disease. Even with comprehensive treatment, patients with schizoaffective disorder are often unemployed, homeless, and poor. The precise cause of schizoaffective disorder is not known, but there are specific changes in the brain along with genetics as contributing factors.

Schizoaffective disorder is a life-long disease. The psychotic symptoms and mood swings associated with schizoaffective disorder are not predictable. While the goal of treatment is to reduce psychiatric and social impairment caused by psychosis, hallucinations, and delusions, even when using the most effective treatments such as antipsychotic medicines and mood-stabilizers, such as Depakote, psychiatrists often are only able to reduce psychotic symptoms, but rarely eliminate them. One of the primary goals of treating patients with schizoaffective disorder is to keep them out of institutions/hospitals and to try to keep them together with their families in the community.

Antipsychotics are the first-line treatment of choice for patients with schizoaffective disorder. However, the majority of schizoaffective disorder patients are on multiple psychotropic medications, which are necessary to prevent psychiatric institutionalization and often save their lives. Depakote is utilized as an effective and medically necessary treatment at times for the severe mood swings associated with schizoaffective disorder, just as it is often used for bipolar disorder. Lithium, Lamictal, and Tegretol, although also classified as mood-stabilizers, have not been shown to be as effective as Depakote in the treatment of mood swings associated with schizoaffective disorder, particularly as of 1999.

Most patients with schizoaffective disorder require treatment with more than one psychotropic medication. The manifestations of schizoaffective disorder usually change over time, and are often unpredictable. The choice of medications for a patient with schizoaffective disorder can change over time depending on their symptoms. I was first licensed as a medical doctor in 1983 and became board-certified as a psychiatrist in 1988. I am familiar with the standard of care in prescribing medicines for patients with schizoaffective disorder (including in 1998-2000) as a result of my education, training, teaching responsibilities as a professor, and thirty years of clinical practice.

My fee for review of medical records and for preparing reports is $ 575.00 per hour. A copy of my curriculum vitae is attached to this report as Exhibit A. Exhibit B contains a list of my expert deposition and trial testimony in the past four years.

You have asked that I review the medical and psychiatric records for Ms. Irina Burnett, a 49-year-old woman who has been treated since the 1990s for schizoaffective disorder. Prior to forming opinions in this matter, I reviewed the following documents:

Records from Greenville County Health Department, South Carolina Department of Health and Environmental control
Records from Greenville Mental Health Center, Greenville, South Carolina
Medicaid records of South Carolina regarding Irina Burnett (prescription records)
Records from Greenville Memorial Hospital

Records from Connie Maxwell Children's Home
Pharmacy Records
Deposition transcript of Al C. Edwards, M.D., taken on October 3, 2016
Deposition transcript of Irina Liona Burnett, taken January 24, 2017
Deposition transcript of Danny Burnett, taken June 15, 2017 (DOB: 4/15/60)
Deposition transcript Clare H. McLain, MSN, taken August 10, 2017

Review of Medical Records

Ms. Irina Burnett suffers from a severe form of schizoaffective disorder. Records from Greenville Mental Health Center in South Carolina indicate that in December 1997, Ms. Burnett was originally diagnosed with Schizoaffective Disorder, 295.70, and presented with "hallucinations, depression, suicide attempts." She had a history of alcohol abuse and "rule out borderline" personality disorder. She was homeless, and it was noted she had been in foster homes since the age of three. Her medications on December 10, 1997, consisted of Clozaril, an antipsychotic medicine for schizoaffective disorder; Prozac 20 mg daily for treating depression; and Cogentin 1mg twice daily for the side-effects of Clozaril such as extrapyramidal (nerve) symptoms.

In 1998, Ms. Burnett's psychotic symptoms appeared to have worsened and deteriorated. On February 10, 1998, Dr. Earnestine Otovo-Leach, M.D., a psychiatrist, noted that Ms. Burnett,

> *"Is a 29-year-old female who was previously treated at Greer Mental Health Center. She states she is currently homeless and living in Tyndale House. She previously had been diagnosed with having Schizo-affective disorder; she also has a history of abuse of alcohol and other substances."*

On March 5, 1998, Ms. Burnett was assessed by a psychiatrist, Dr. Karen Pratt. She was "somewhat depressed, anxious, seeing ghosts, having increased startle reflex. Occasionally hears voices commanding self-harm, but has been able to resist these and can contract. She seems to have delusional ideas either/or myths about her early family history." At this visit, Ms. Burnett's antipsychotic medicine, Clozaril, was increased to 50 mg each morning and 275 mg each night. She remained on Prozac and Cogentin.

Two weeks later, on March 19, 1998, Ms. Burnett was seen again at Greenville Mental Health Center where she noted she learned that her mother, whom she had not seen for about a year, had attempted suicide.

On July 29, 1998, Dr. Pratt noted that Ms. Burnett had additional, intrusive thoughts of hurting herself. She made a tiny superficial cut under her left fifth finger. She seemed a bit slower in expressing thoughts and finding some words. Her mood was also somewhat depressed. The plan was to increase her Clozaril.

On August 4, 1998, Dr. Otovo noted that Ms. Burnett was stressed at work and cut herself with a razor. She continued to have auditory hallucinations. She was instructed to increase her Cogentin and continue with Clozaril and Prozac.

On September 2, 1998, during an initial visit with Ms. Burnett, Dr. Al Edwards, a psychiatrist, noted the following history in Ms. Burnett's medical record,

> *"…claims she had some seizures with loss of consciousness some six years ago, remembers having and [sic] EEG and can describe it to me but does not remember where it occurred. Since this person demonstrates command type hallucinations which are not associated with behavior at this point but have been associated in the past, such as the age of 19. She chased her family around with a butcher knife after the voice told her to do so. It is imperative that we try to get the best handle we can on this persons [sic] illness."*

Years later, Dr. Edwards testified in his deposition on October 3, 2016, that when he first evaluated Ms. Burnett on September 2, 1998, in addition to a diagnosis of schizophrenia, Irina Burnett had "possibly some hypoxic brain injury secondary to a suicide attempt several years ago."

On September 30, 1998, Ms. Burnett saw Dr. Edwards for a follow up appointment. She was taking Clozaril, Prozac, and Cogentin.

On November 18, 1998, Dr. Edwards saw Ms. Burnett again. During that appointment, Dr. Edwards noted decreased memory and concentration in Ms. Burnett, possibly secondary to her medications (Clozaril, Cogentin and Prozac). He noted the following,

> *"…we explored an interesting phenomenon; she says that on occasion, several times a week, for about 15 minutes she will see a green halo, sort of an aura around things in florescent green color. She says it lasts for about 15 minutes and then will go away. During this time she has trouble putting her thoughts together and has decreased concentration. She also tells me that a year or so ago when she was working at the Marriott Hotel, on two occasions she had two episodes of lost consciousness, where the other staff people said she fell down, jerked for a while and then came to with no memory of the event. This is interesting because her older brother has seizures, her father actually died from complications of seizures. He had a seizure, fell, hit his head, and had enough head trauma to die from that. We are going to go ahead and order an EEG. I wonder if these things are seizure equivalent problems. In addition, another interesting thing was noted that she has a very minimal tic. We will investigate these, get an EEG and she her again in six weeks."*

On January 6, 1999, Dr. Edwards saw Ms. Burnett for a follow up appointment. At that time, Dr. Edwards noted that Ms. Burnett was not pregnant and "risk discussed." He then wrote,

> *"Without a lot of difficulty she has had some of the peculiar episodes where she develops an aura and some visual illusionary kind of experiences. Her EEG which we had done was abnormal. It did show some spiked patterns. She did not have a full-blown seizure but there was some significant abnormalities on her EEG. Given the history that her father and brother both had seizure disorder, we are going to start her on Depakote 250 mg, bid [twice daily] today and see her again in a week. At that time we may consider tapering her Prozac."*

Dr. Edwards testified that he prescribed Depakote on this date as a dual treatment for a possible seizure disorder and a bipolar-type component of schizoaffective disorder. (Dr. Edwards' dep. at 74-75, 124).

With respect to her potential seizure disorder, Ms. Burnett testified, and the medical records reflect, that she experienced seizures with a loss of consciousness in 1992. (Burnett dep. at 115). Ms. Burnett also testified, and the medical records reflect, that she had two episodes of loss of consciousness about a year prior to a doctor's visit in 1998 where she fell down, jerked for a while and regained consciousness with no memory of the event. (Burnett dep. at 119). Ms. Burnett testified that she believes she heard one of her doctors use the term grand mal seizures to describe her seizure condition. (Burnett dep. at 168).

Dr. Edwards saw Ms. Burnett one week later on January 13, 1999 and increased Depakote to 500 mg twice daily,

> *"Doing pretty well on the Depakote. Says that all her unusual experiences, such as halos and the unusual complex seizure-type phenomenon have disappeared since she has been on the Depakote. She is getting a bit stressed out at work, however. She is watching 30 + animals on each Thursday and that is a bit much for her and as a consequence she is occasionally experiencing some auditory and visual illusion, seeing shadows of animals, feeling them brush up against her when they are not there. I advised her to talk to her boss about the work that she is doing to see if they could maybe lighten up on her just a bit. There are no symptoms of depression or suicidality. We are going to decrease her Prozac to 10mg and then discontinue it after a week. We will see her again in six weeks."*

Ms. Burnett was subsequently seen on February 17, 1999 by Dr. Edwards, who noted,

> *"…reports some improvement since beginning Depakote with only an occasional visual illusion lasting two to three minutes perhaps once per day. The illusion consists of seeing a faint glow around objects. In addition, on occasions she will experience a tactile hallucination such as feeling someone braid her hair. She is experiencing no side-effects from our current medication Clozaril, Depakote, and Cogentin. Her last W.B.C. count was normal. A [sic] most concerned her today was the fact that her common-law husband has a very severe alcohol addiction and Valium abuse. She does not want to leave him although many people have advised her to do so that is interested in getting him some help. I offered family counseling and evaluation and an inpatient treatment for husband. She does not know if he will agree to any of this."*

The next entry from Greenville Mental Health Center dated March 5, 1999 indicates,

> *"Verbal order from Dr. Mattison to stop Depakote secondary to positive pregnancy test."*

On March 10, 1999, five days after receiving instructions to stop Depakote, Dr. Edwards saw Ms. Burnett at Greenville Mental Health Center and documented,

> *"Found out a week or so ago that she was pregnant. We had just started her on Depakote due to an abnormal EEG and some partial seizure type symptoms she was having with auras around things that she was looking at. The Depakote was immediately stopped by Dr. Pratt, appropriately. We have continued her Clozaril. I think the risk benefit ratio favors Clozaril at this time. We are going to stop her Cogentin. Her only medication will be Clozaril 50 mg a morning, 275 mg at night. She is cheerful. Her thought process is generally intact. She has had a few more episodes of these aura-type episodes but no frank loss of consciousness. There are several issues which I have discussed today around her pregnancy. One is the issue of Clozaril, associated with some difficulty with children and babies and we talked about the risk benefit today of that. We also discussed the cats that she has a lot of in the house and her job working at the animal shelter the risk of toxoplasmosis is significant."*

Ms. Burnett was a half pack per day cigarette smoker when she became pregnant. She indicated to her providers that she was not on birth control pills at the time of her conception. Ms. Burnett indicated she had her last two menses on December 8, 1998 and January 6, 1999. She had a positive HCG pregnancy test at the health clinic on March 10, 1999. Her child, Daniel, was born full-term at 38 weeks on , so her estimated date of conception was around the second week of January 1999.

A medical record dated April 14, 1999 entitled *Preventative and Rehabilitative Family Support Services for Primary Care Enhancement,* identified four risk factors for Ms. Burnett's pregnancy,

- Schizophrenia
- Smokes cigarettes
- Use of alcohol in early pregnancy
- Lacks resources

A nurse's note from April 14, 1999 stated Ms. Burnett, "Appears to have adjusted to unplanned pregnancy and receptive to learning good prenatal care." This was Ms. Burnett's first pregnancy. Ms. Burnett's family history was remarkable for her mother, who at the time, was,

> *"In a mental institution and her father is dead. She and three siblings were adopted as children. Reports no relationship with step-parents. She smoked cigarettes, used alcohol in early pregnancy. Denies use of alcohol or drugs at present time. She completed 12th grade. She and father of baby live in rented mobile home with 2 bedrooms, electric heat and smoke alarm."*

> *"She has tactile hallucinations in the form of feeling that something is brushing against her when nothing is there. She also has visual hallucinations in terms of seeing people glowing green color. She has had auditory hallucinations in the past."*

Ms. Burnett was subsequently seen at the Greenville health clinic on April 28, 1999 by a social worker where the following history was noted,

"PHN referral for schizophrenia, lack of infant supplies. Ct [client] had concerns about spina bifida diagnosis on fetus… 31 y o single white female resides with FOB [father of baby] in a two bedroom trailer. Client with current diagnosis of schizophrenia. Client's fetus diagnosed with spina bifida and fluid on the brain. Client has decided to keep the baby. Father of baby employed and extremely involved. Client formerly employed at the animal shelter. Client has a crib but needs other supplies. Client has WIC, Medicaid, SSI, is ineligible for food stamps. Client regularly attends Greenville Mental Health Center and participates in the community rehabilitation and support program. Client has adequate emotional support. Client with no history alcohol dependence; past marijuana use. Client denies current use. Client currently smokes 1-2 cigarettes/day. EDC 8 October 99. Client has a mental health counselor who attends with all appointments, etc."

"Summary: 31 y/o SWF who receives mental health treatment every day. Client also mentally disabled."

On May 12, 1999, Dr. Edwards noted that she had been experiencing psychotic symptoms, more so since Depakote was discontinued.

On May 26, 1999, Dr. Edwards noted that Ms. Burnett had some auditory and visual hallucinations. She also felt a ghostly figure in the form of her father was talking to her, and she was hearing negative voices.

On June 9, 1999, Dr. Edwards noted that Ms. Burnett had an increase in psychotic symptoms, particularly visual hallucinations and illusions of bugs on her. He wanted to increase her Clozaril.

On June 23, 1999, Dr. Edwards noted that a complaint Ms. Burnett had before she was put on Depakote (feeling the ground beneath her coming to alive) had returned.

On August 18, 1999, Dr. Edwards noted that Ms. Burnett was having more auditory illusions and frank hallucinations and voices telling her that she doesn't need help or to be around people. She felt like she was being buried alive and floating. Dr. Edwards increased her Clozaril.

On September 8, 1999, during an OB visit, Dr. Valerie Skinner noted that Ms. Burnett had a reported seizure that lasted 30 seconds where she was disoriented with no loss of consciousness.

On September 16, 1999, Dr. Edwards noted psychotic symptoms of Ms. Burnett feeling that she was being burned alive, voices telling her to harm herself, and that her baby is a dog. He did not increase Clozaril. Dr. Edwards noted a peculiar episode a week before where she became ashen with some minor seizures possibly related to gestational diabetes.

On September 17, 1999, during a nutrition consultation, E. Collins, RD (Registered Dietician) noted that Ms. Burnett suffered "psychotic episodes – threatened stabbing self and baby yesterday."

On , Ms. Burnett gave birth to a son, Daniel, who had spina bifida and hydrocephalus.

Ms. Burnett continued her mental health care at the Greenville Mental Health Center.

On November 10, 1999, Dr. Edwards wrote that Ms. Burnett's thought process revealed some disturbing ideas as well as hallucinations. She reported hearing a voice telling her to stab and kill herself while she was washing dishes. She also reported hearing a voice telling her to pick up her baby (Daniel) and throw him on the ground and kill him. Dr. Edwards noted that Ms. Burnett was "certainly placing herself and her baby at risk with the exacerbation and requires hospitalization." Depakote was restarted either by Dr. Edwards during the November 10 encounter or during Ms. Burnett's subsequent hospitalization at Harris Hospital. Dr. Edwards testified that Depakote was likely restarted at that time because of the belief that Depakote would help Ms. Burnett's condition. (Dr. Edwards dep. at 144-146).

Ms. Burnett remained on Depakote (as well as other medications including antipsychotics and anti-depressants) from 2000 through the present for necessary treatment of schizoaffective disorder.

Opinions/Conclusions

Following a review of medical records, psychiatric records, depositions, and other materials regarding Irina Burnett, I have formed the following opinions based on a reasonable degree of medical certainty:

1) Irina Burnett has schizoaffective disorder. Ms. Burnett meets the DSM-IV diagnostic criteria for schizoaffective disorder (295.70) because of her major depressive episodes, delusions and hallucinations for at least 2 weeks in the absence of prominent mood symptoms, symptoms of a mood episode present for a substantial portion of the illness, and the disturbance is not due to the physiological effects of a substance or a general medical condition. While some records stated that Ms. Burnett had schizophrenia, Dr. Edwards recognized Ms. Burnett as having schizoaffective disorder, consistent with the records and the diagnostic criteria.

Schizoaffective disorder is on a spectrum between schizophrenia and bipolar disorder, but is neither of these conditions. Dr. Edwards also believed that Ms. Burnett had symptoms of a seizure disorder such as partial complex seizures. Dr. Edwards noted the history that Ms. Burnett had a possible hypoxic brain injury secondary to a history of suicide attempts, which may explain why she had an abnormal electroencephalogram (EEG). In addition to psychotic psychiatric symptoms, Ms. Burnett had persistent symptoms of tactile hallucinations, experienced visual auras, and had other symptoms suggesting temporal lobe epilepsy or a similar seizure category disorder.

Although Ms. Burnett did not have bipolar disorder per se, she did have symptoms that constituted the affective component of a schizoaffective disorder. Schizoaffective disorder is one of the most severe of psychiatric disorders, afflicting millions of people worldwide. Schizoaffective disorder is just as serious a condition as bipolar disorder. Much like bipolar disorder, schizoaffective disorder is a life-long psychiatric illness. Reliable estimates of completed suicides in bipolar patients indicate that as many as 19% (Bowden, Fawcett, 2003) may eventually end their lives by suicide. (See also, DSM-5, p. 131 "The lifetime risk of suicide in individuals with bipolar disorder is estimated to be at least 15 times that of the general population. In fact, bipolar disorder may account for one-quarter of all completed suicides").

Untreated schizoaffective disorder is considered a life-threatening medical condition. At times, Irina Burnett's schizoaffective disorder has caused her to have severe symptoms including suicidal preoccupations, suicide attempts, homelessness, hospitalizations, and lack of employment. Sadly, much of what she has experienced is based on life-disrupting, psychotic delusions. She will require treatment for schizoaffective disorder for the rest of her life.

2) As of January 1999, Dr. Edwards testified he prescribed Depakote because he believed Depakote was the best choice of medication for Ms. Burnett for its potentially beneficial mood-stabilizing abilities, and simultaneously, as an anti-convulsant for symptoms of a probable seizure-like condition that caused Ms. Burnett difficulties almost every day. Ms. Burnett had a significantly abnormal EEG confirming epileptiform spiking activity in her brain. Dr. Edwards testified that he was not aware of any dual purpose drug that would potentially do what Depakote did — treat both conditions, her schizoaffective disorder and her seizure disorder. (Dr. Edwards' dep. at 84). Dr. Edwards could not identify another treatment regimen that he thought was more reasonable than Depakote. (Dr. Edwards' dep. at 125).

I agree. In my opinion, the prescribing of Depakote for Irina Burnett by Dr. Edwards was medically necessary and met the standard of care for treatment of her seizure disorder and her schizoaffective disorder. I have treated many patients with schizoaffective disorder with a history of seizures and have prescribed Depakote for both conditions. Dr. Edwards' prescribing decision was appropriate, particularly because Depakote was also an established, well-known treatment choice for schizoaffective disorder, including the severe mood swings associated with the disorder.

In 1999, Depakote was recognized as a necessary, effective, and reliable medication for seizure disorders, schizoaffective disorder, and many bipolar patients. (McElroy 1989, McElroy 1993, Stoll 1994, Guay 1995). Ms. Burnett required the prescribing of Depakote in 1999, chosen by her physician as the best option under the circumstances in order to stabilize her mood, address her seizure disorder, and minimize her risk for suicide.

The psychiatrists and staff at Greenville Mental Health Center who treated Ms. Burnett faced difficult decisions about treating her potential seizure disorder and schizoaffective disorder in order to preserve her quality of life and reduce the risk of death by suicide. All medications prescribed by doctors for seizure disorders and schizoaffective disorder like Ms. Burnett's in 1999 were known to carry recognized risks in pregnancy. At the same time, choosing not to treat a patient such as Ms. Burnett is not acceptable, and can lead to severe functional impairment, death by suicide, and potential harm to others. Without such treatment, there was a distinct possibility that Ms. Burnett was at a higher risk for suicide and for becoming even more dysfunctional. The prescribing of schizoaffective disorder and bipolar medicines for women in their child-bearing years, even with known risks and potential side-effects, has been instrumental in helping many patients lead fuller, safer, and more productive lives. (DSM-5; Hirschfeld).

The choice of Depakote for Ms. Burnett in January and February 1999 provided the expected benefit of controlling her schizoaffective disorder and may have saved her life. It also provided the benefit of controlling any seizures that Ms. Burnett was suffering.

Even after the birth of her son, Ms. Burnett and her physicians thought she benefitted so significantly from Depakote that she went back on it shortly after the birth of her son in November 1999. Ms. Burnett has remained on Depakote since restarting the medicine in November 1999. The fact that Ms. Burnett resumed Depakote in 1999 and has remained on it through the present supports the conclusion that Depakote was (and still is) a necessary and successful choice for managing her life-long psychiatric disorder and simultaneously, addressing her abnormal EEG.

The medical records support the conclusion that Depakote has worked well for reducing Ms. Burnett's mood swings, psychotic delusions and hallucinations, improving her mood, and potentially reducing her risk of suicide. Depakote has had an overall positive impact on her quality of life. Additionally, medical records support the conclusion that Depakote also worked well for reducing Ms. Burnett's seizure activity.

3) In light of her abnormal EEG and concurrent schizoaffective disorder, there was little if any scientific basis to suggest a reasonable alternative medication other than Depakote for Ms. Burnett in 1999. Accordingly, Depakote was not only a reasonable option, but it was the best option for Ms. Burnett in 1999.

Lithium is an alternative treatment option frequently prescribed for bipolar patients, but rarely prescribed for patients with schizoaffective disorder for which Lithium is often ineffective. (May 1988, Grof 1998, McElroy 1999). Lithium has no benefit for treating seizures, and therefore, is not used to treat seizures, and would not have been a reasonable choice for Ms. Burnett in 1999.

Tegretol (Carbamazepine) is a mood stabilizer in the anti-convulsant class that has been prescribed for relatively few patients with schizoaffective disorder or bipolar disorder. Tegretol is used infrequently by psychiatrists for a number of reasons. Tegretol is sedating. It causes weight gain. It is classified as a tricyclic class medicine and often causes dry mouth, constipation, dizziness, fainting, and urinary retention. Taken in overdose quantities, Tegretol is often fatal with as little as a fifteen day supply of the medicine. A patient such as Irina Burnett, who had a history of suicide attempts, would be a poor candidate for Tegretol.

Lamictal was first approved for the treatment of bipolar disorder in 2003. Lamictal's utility for schizoaffective disorder in 1999 was not scientifically established and would generally be unknown to most treating psychiatrists in 1999.

Atypical antipsychotic medications are frequently used in conjunction with other medications to treat schizoaffective disorder. Atypicals, however, are not used to treat seizures and are generally not used as monotherapy for either schizoaffective disorder or bipolar disorder. Ms. Burnett was prescribed Clozaril in 1998 and 1999 with limited success. She subsequently was prescribed multiple other antipsychotic medicines over

many years and in almost every regard, required Depakote and/or other medications to manage her severe psychiatric symptoms. Atypical antipsychotic medications also can carry a risk of serious side-effects to the patient, including causing diabetes, an increased risk of strokes, agranulocytosis, sudden cardiac death, blood clots, tardive dyskinesia, and fatal neuroleptic malignant syndrome.

Antidepressant medicines are not used to treat seizures and are almost never used as monotherapy in schizoaffective disorder. They are often utilized during depressive phases to treat symptoms such as those in Ms. Burnett. Antidepressants also have a risk of serious side effects to the patient including sedation, cognitive impairment, weight gain, sexual dysfunction, and cardiac side effects.

4) Physicians must make decisions weighing the risks and benefits of any treatment for a patient, including treatment of schizoaffective disorder and bipolar disorder, in women who are at risk for becoming pregnant or who intend to become pregnant. The primary goal of the psychiatrist is to control the symptoms of schizoaffective disorder and severe mood disorders. If a medicine such as Depakote is successful in controlling a patient's symptoms, as appears to be the case with Irina Burnett, then the physician's role is to ensure that the patient is advised of the risks if the patient should become pregnant.

Dr. Edwards testified that he was aware of the risk of spina bifida and birth defects with Depakote. Although Ms. Burnett said she has no recollection of Dr. Edwards, Dr. Pratt, or the staff at Greenville Mental Health Center explaining to her that there were birth defect risks with her taking Depakote prior to the pregnancy at issue, Ms. Burnett's medical records reflect at least one occasion where "risks discussed" were the focus of a conversation between Dr. Edwards and Ms. Burnett. Dr. Edwards testified that his standard practice in January 1999 was to tell patients prescribed Depakote, if you get pregnant, "your baby can have birth defects and some of them can be serious." Dr. Edwards testified that is the sort of discussion he would have had with Ms. Burnett. (Dr. Edwards' dep. at 131-132).

Dr. Edwards' standard practice would have also been to inquire as to whether Ms. Burnett was using birth control and to stress the importance of continuing to use some sort of effective birth control. (Dr. Edwards' dep. at 133). When Dr. Edwards first prescribed Depakote for Ms. Burnett, she denied being pregnant. Her last menstrual period was recorded as January 6, 1999, the same day Dr. Edwards prescribed Depakote for her.

5) It has been recognized in the Depakote labeling, in the medical literature, and in the psychiatric community for decades that Depakote, also known by its generic formulation as Valproate, can cause teratogenic effects, including neural tube defects. As one example, in the textbook *Drug Evaluations, Sixth Edition*, published by the American Medical Association in September 1986, Depakote was recognized for its teratogenic effects and was designated as Pregnancy Category D by the Food and Drug Administration (FDA).

As of 1999, Depakote was widely recognized in the psychiatric community as being associated with a higher incidence of neural tube defects than any other medication used to treat bipolar disorder or schizoaffective disorder. The 1 to 2% risk of spina bifida with maternal Depakote use was well known in the psychiatric community to be far higher than

the background risk of spina bifida in the general population. As a practicing physician and psychiatrist, it is widely known and I was taught in my medical training, that neural tube formation in utero occurs within about the first twenty-eight days following ovulation or conception.

The prescribing information for Depakote adequately informed doctors as of 1999 of the birth defect risks associated with Depakote. Abbott Laboratories made it clear to physicians in the medicine's prescribing information that Depakote was classified as Pregnancy Category D, meaning, according to the FDA, that there is positive evidence of human fetal risks, but potential benefits may warrant the use of the drug in pregnant women despite potential risks. Depakote prescribing information as early as the mid-1980's stated that Depakote could produce teratogenic effects including neural tube defects such as spina bifida.

The prescribing information for Depakote provided much more information about birth defects than any other medication used to treat schizoaffective disorder or bipolar disorder and would convey to physicians that Depakote had a higher risk compared to other medications that treat these conditions. Beginning in 1996, there was a black box warning in the Depakote label stating it can produce teratogenic effects, including spina bifida. Dr. Edwards knew this in 1999. (Dr. Edwards' dep. at 94). According to the FDA approved label, the benefits of its use must be weighed against the risk of injury to the fetus. These warnings were clear, adequate, and widely available to all physicians, including psychiatrists treating bipolar disorder and schizoaffective disorder, to inform them about the risks of the medication. Moreover, these warnings conveyed to physicians that Depakote presented a risk for pregnancy that was different and more significant than that presented by other medicines for the treatment of bipolar disorder and schizoaffective disorder. Depakote was the only treatment option for bipolar disorder or schizoaffective disorder that carried a black box warning for birth defects.

The Depakote prescribing information in 1999 also had a separate 10-paragraph section called *Usage in Pregnancy*, which reported "the risk of valproic acid exposed women having children with spina bifida to be approximately 1-2%." The Depakote prescribing information further stated that there was a risk of other possible congenital abnormalities including cranial facial defects, cardiovascular malformations, and other abnormalities. Dr. Edwards knew the foregoing in 1999. (Dr. Edwards' dep. at 105-106).

The 1-2% risk of spina bifida stated in the prescribing information was the most scientifically reliable data available as of 1999. The 1-2% risk has been confirmed by later data (Jentink 2010; Hernandez-Diaz 2012). In view of the totality of the evidence, there is no reliable basis for an estimate other than the 1-2% stated in the warning label.

The 1-2% rate for spina bifida is also the most appropriate information for a doctor to use in counseling patients. Psychiatrists know that the 1-2% risk for spina bifida far exceeds the background rate in the normal population. The Depakote prescribing information in 1999 stated that the incidence of spina bifida in the general population is 0.1% to 0.2%. Dr. Edwards testified that the 1999 Depakote prescribing information communicated that the

risk of spina bifida with Depakote use was at least 10 times higher than the background rate in the general population. (Dr. Edwards' dep. at 100-101).

By 1999, it was widely publicized in the literature and known in the psychiatric community that Depakote had a particular risk of spina bifida that other medications used to treat schizoaffective disorder and bipolar disorder did not.

Additionally, as of 1999, there was insufficient reliable scientific information to make a statement about Depakote's overall risk of birth defects or the relative teratogenicity of Depakote compared to other anti-epilepsy drugs (AEDs), most of which are not used to treat schizoaffective disorder or bipolar disorder patients. The North American Anti-Epileptic Drug (NAAED) pregnancy registry was in its infancy and results were not published until many years later and well after Daniel Burnett was born. Final results from this registry were not published until March 2005.

For any medication with a risk of birth defects, it is generally thought by psychiatrists that the risk may increase as the dose increases. It is also generally accepted to use no more medication than is required to achieve therapeutic benefit. The risk of birth defects can also increase if more than one drug with a risk of birth defects is taken at the same time. This is basic medical information that did not need to be included in any warning.

6) The prescribing information provided by Abbott gave physicians such as Dr. Edwards, Dr. Pratt, the staff at Greenville Mental Health Center, and me sufficient and accurate information to make appropriate prescribing decisions for their patients such as Ms. Burnett. In addition to the prescribing information provided by Abbott, psychiatrists are taught to rely upon information in the medical literature as well as from their own research, reading, and continuing medical education.

I am available to interview Ms. Burnett in a face-to-face diagnostic psychiatric examination and would welcome the opportunity to do so. I also reserve the right to supplement my opinions if additional information becomes available.

Sincerely,

Christopher B. Ticknor, M.D.

CBT/kl